REMARKS

Applicant is filing this Amendment and Response in response to the Final Office Action dated September 29, 2005 and to the Decision on Appeal decided August 31, 2007. At the time of the Final Office Action, claims 1-5, 8-21, 30-33, and 35-39 were pending. By the previously-submitted Response (filed on November 29, 2005) to the Final Office Action, Applicant cancelled claims 13-21, 38, and 39, and therefore, only claims 1-5, 8-12, 30-33, and 35-37 were pending on the subsequent appeal.

By the present Paper, Applicant amended claims 1, 30, 32, 36, and 37, cancelled claims 10 and 11, and added new claims 40-42 to clarify features of the present techniques and to expedite prosecution. Thus, claims 1-5, 8, 9, 12-21, 30-33, 35-37, and 40-42 are now pending in the present application.

New Claims

New claims 40-42 are generally directed to using low resolution Raman to monitor the trimerization of ethylene monomer to 1-hexene product. Support for the new claims can be found in the specification, for example, at page 8, line 6 – page 9, line 7. Applicant respectfully request favorable consideration and allowance of the new claims.

Claim Rejections under 35 U.S.C. § 103(a)

In the Final Office Action, the Examiner rejected claims 1-5, 8-11, 13-21, 30-33, and 35-39 under 35 U.S.C. § 103(a) as obvious over Lashier et al. (U.S. Patent No. 5,689,028) in view of

Alsmeyer et al. (U.S. Patent No. 5,638,172). The Examiner rejected claims 12 and 37 under 35 U.S.C. § 103(a) as being unpatentable over Lashier et al. and Alsmeyer et al. in further view of Tanaka et al. (U.S. Patent No. 5,750,817). Claims 1 and 30 are independent. Applicant respectfully traverses these rejections.

Applicant still maintains that none of the cited references disclose a *low-resolution* Raman spectrometer, as recited in independent claims 1 and 30. Applicant also believes there is no appropriate reason to modify the Lashier 1-hexene process to incorporate a *low-resolution* device, as proposed by the Examiner. *See* Final Office Action, page 4. Applicant has further stated that one of ordinary skill in the art would not find an appropriate reason to modify the Lashier reference to read on the present claims in light of the closeness of the spectral peaks of the ethylene monomer and the 1-hexene product. However, the BPAI noted that Applicant's contention was unpersuasive because the claims on appeal were not limited to producing *1-hexene product from ethylene*. *See* Decision on Appeal, page 8.

Thus, to advance prosecution of the present application, independent claims 1 and 30 have been amended to incorporate the reaction of *ethylene* monomer into *1-hexene* oligomer product. Therefore, clearly, the skilled artisan would not find an appropriate reason to modify the Lashier reference (to incorporate low-resolution Raman spectrometry in the production of 1-hexene from ethylene) to read on the present claims. Indeed, in light of the closeness of the spectral peaks of the ethylene monomer and the 1-hexene product, one of ordinary skill in the art, without the benefit of Applicant's disclosure, would <u>dismiss</u> *low-resolution* Raman spectrometry

in such a modification of Lashier because the peaks of ethylene (1620 cm^{-1}) and ethylene (1640 cm^{-1}) are so close. *See, e.g.*, Application, page 4, lines 3-13 ("Thus, it would appear necessary to employ high resolution Raman spectrometry equipment to analyze the components of the hexene preparation process.") (emphasis added); page 15, lines 1-10; page 18, line 4 – page 19, line 2.

Applicants also note that objective evidence of such conclusions is disclosed, for example, in the article "Low-Resolution Raman Spectroscopy," Spectroscopy 13(10) 1998, which is referenced in the present application on page 5 at lines 30-34. *See* Decision on Appeal, page 8 (asserting that Appellant did not offer any objective evidence). The referenced article concludes with statements indicating that low resolution Raman spectroscopy (LRRS) may not have sufficient resolution for systems wherein the peak separation is less than 30 cm^{-1}. *See* "Low-Resolution Raman Spectroscopy" at page 35. Applicant has attached a copy of the article.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejection of the claims. It should be noted that with regard to the rejection of dependent claims 12 and 37, the Tanaka reference does not obviate the deficiencies of the Alsmeyer and Lashier references discussed above with regard to the independent claims. Therefore, rejected claims 12 and 37 are believed to be patentable over the cited combination at least by virtue of their dependency on an allowable base claim. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 12 and 37 and allow the claims.

Conclusion

In view of the remarks set forth above, the Applicant respectfully requests reconsideration of the Examiner's rejections and allowance of all pending claims 1-5, 8, 9, 12-21, 30-33, 35-37, and 40-42. If the Examiner believes that a telephonic interview will help speed this application toward issuance, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: October 31, 2007

Floron C. Faries
Reg. No. 59,991
FLETCHER YODER
P.O. Box 692289
Houston, TX 77269-2289
(281) 970-4545

Low-Resolution Raman Spectroscopy

Richard H. Clarke,*
Sameer Londhe, and
M. Edward Womble
Boston University
Photonics Center
8 Saint Mary's Street
Boston, MA 02215-2421

*To whom correspondence should be addressed. He can also be reached via e-mail at *clarke@chem.bu.edu.*

The concept of low-resolution Raman spectroscopy (LRRS) is introduced as a potentially highly useful, low-cost approach to organic analysis. As an analytical tool, LRRS is similar to near-IR, in that it uses broad vibrational bands of the system of interest for identification and characterization. Examples of organic mixtures run by LRRS at low resolution are presented to illustrate the point that even though all spectral features are not necessarily cleanly resolved with either near-IR or LRRS, the ability to use vibrational bands as fundamentals, rather than overtones, gives LRRS an inherent analytical advantage over near-IR.

Vibrational spectroscopy, the identification of organic compounds via their characteristic vibrational fingerprints, has been one of the mainstays of analytical chemistry over the past 50 years and is still a very active analytical tool. Recent developments in optics, filters, detectors, lasers, and software are resulting in the rapid expansion of two areas of vibrational spectroscopy: near-infrared and Raman spectroscopy. These advances are moving the techniques out of the labs of a few specialists and into the rapidly expanding fields of process control, product quality control, medical diagnostics, and environmental monitoring.

The chemical analysis of materials containing organic components either as the main constituent (e.g., hydrocarbon fuels, solvent mixtures, organic process streams, etc.) or as a contaminant (e.g., in aqueous solutions) is often determined by optical spectral analysis. For this purpose, near-IR analysis has become a very popular method despite the technique's inherent lack of resolution. Powerful software routines for analyzing broad spectral features have allowed near-IR for chemical analysis to move forward rapidly while making use of the natural advantages of the near-IR technique, such as fiberoptic delivery and collection of signal, along with inexpensive light sources and detectors.

Raman spectroscopy has long been recognized as an analytical tool with much promise. It has the potential for delivering the kind of detailed spectral analysis of organic systems — particularly organic liquids — that historically has been the hallmark of mid-IR spectroscopy. The sharp detail of the fingerprint region and subsequent ease of analysis provided by mid-IR is, in principle, available in a Raman spectrum as well. The main drawback to Raman has been its high price tag relative to mid-IR and near-IR.

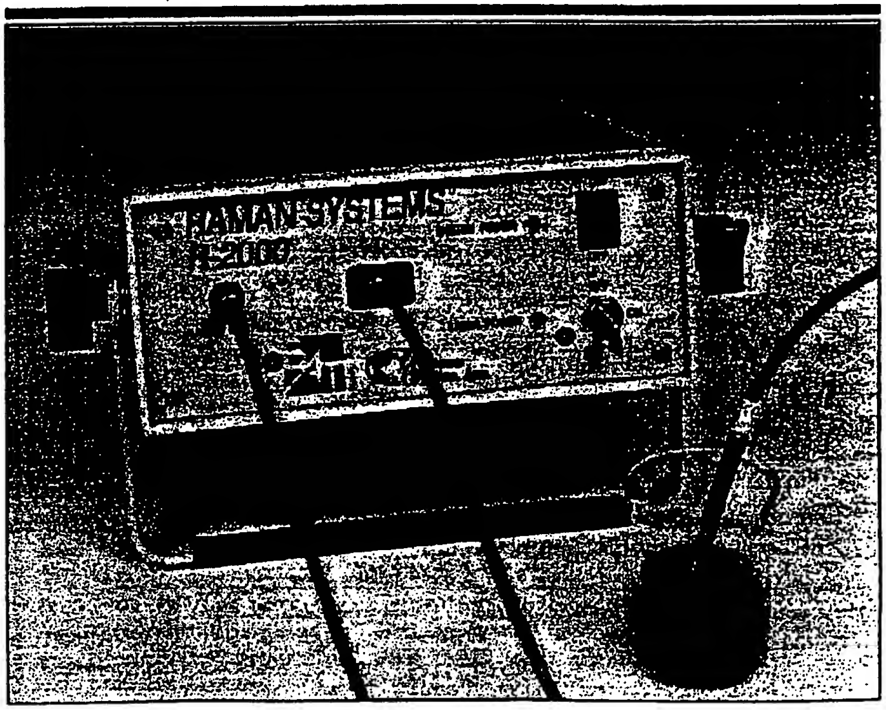

Figure 1. The Raman R-2000 spectrometer.

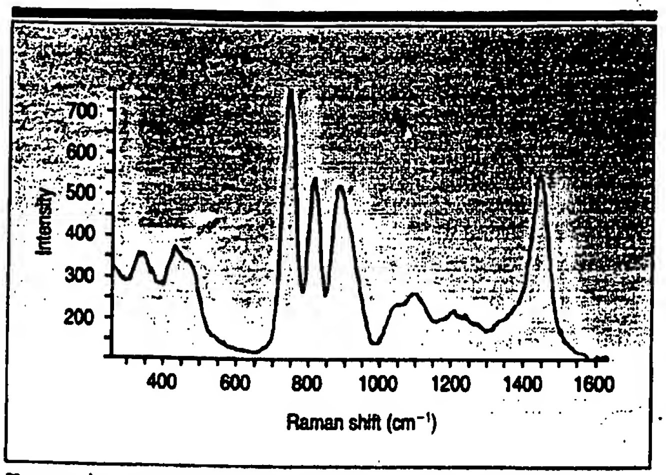

Figure 2. Low-resolution Raman spectrum of 1:1:1 mixture of ethanol, 2-propanol, and 2-methyl-2-propanol.

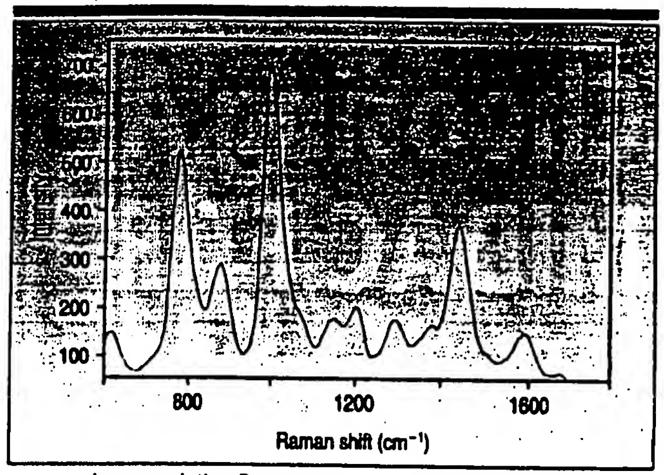

Figure 3. Low-resolution Raman spectrum of a 1:1 mixture of toluene and *n*-hexane (laser bandwidth ~30 cm^{-1}).

To a large extent the price barrier to Raman is lessening. But the main issue is still the laser system required to produce quality high-resolution spectra. Even with the arrival of the laser diode as the scattering source, the laser remains one of the main expenses in developing cost-effective Raman systems.

In this article we introduce the concept of low-resolution Raman spectroscopy (LRRS) as a potentially highly useful, low-cost approach to organic identification and analysis. As an analytical tool, LRRS is similar to near-IR in that it uses the identifying vibrational bands of the system of interest as fundamentals rather than overtone features. Even though all spectral features are not necessarily cleanly resolved with either near-IR or LRRS, the ability to use vibrational bands as fundamentals gives LRRS an inherent advantage over near-IR.

The solid state laser revolution has introduced several important laser sources into Raman analysis. For high-resolution Raman systems the laser line width must be severely controlled, often adding to the cost of the excitation source. For LRRS, however, the strategy of relinquishing resolution details in favor of emphasizing essential identifying basic spectral features simultaneously lessens the demands on the excitation source.

In a typical LRRS application the need for feature separation is much like that encountered in mid-IR spectroscopy. One rarely requires single wavenumber resolution to find the fingerprint feature that allows identification and quantification of the system under analysis. Similarly, in LRRS, the approach uses fundamental frequencies — even if not fully resolved — in the spectral analysis; therefore, a broader band laser source may suffice for the Raman analysis. In this case simpler multimode, solid-state laser sources are both sufficient for the task and extremely cost-effective.

As an example, the complete LRRS system could consist of an inexpensive multimode laser diode, often with a higher power (>500 mW) output than traditional single-mode Raman sources, a low-resolution monochromator matched to a simple CCD detector, with Rayleigh filtering provided by widely available, highly efficient notch filters capable of removing the excitation source background. Such a system has been built into a commercial product, the Raman R-2000, manufactured and marketed jointly by Ocean Optics, Inc. (Dunedin, FL) and the Raman Systems Division of Boston Advanced Technologies, Inc. (Marlboro, MA). Figure 1 shows the Raman R-2000 system.

We have tested the LRRS approach for the analysis of organic materials at the Boston University Photonics Center on a range of organic systems with the Raman instrument. A simple seven-around-one bundled fiberoptic immersion probe (Visionex, Inc., Warner Robins, GA) was used to collect the spectra. The Raman R-2000 system contains a 500-mW, 785-nm multimode laser diode as the excitation source, coupled to an S-2000 monochromator, to provide its Raman signals. The system is fully packaged and ready to provide Raman analysis without further modification. The system was also run with other fiberoptic probes for sample collection.

In a series of organic samples, we examined the LRRS features of the samples with the Raman system. The systems chosen are described below.

MIXTURES OF ORGANIC LIQUIDS

The simplest system in which to demonstrate the LRRS approach is often performed by a variety of vibrational spectroscopic techniques, particularly near-IR analysis. Identifying the components in an organic mixture, in this case an alcohol mixture, provides a sense of the capability and advantage of LRRS.

We prepared a mixed solution of alcohols from 33% ethanol, 33% 2-propanol, and 33% 2-methyl-2-propanol (Aldrich Chemicals, Milwaukee, WI). These alcohols were selected because of their signature C_n-O skeletal vibrational band in the Raman spectrum (1). With the low-resolution Raman system described above and an integration time of 20 seconds, we obtained the spectrum shown in Figure 2 for the mixture.

The figure shows the characteristic C_n-O Raman band for each alcohol clearly resolved in the LRRS. The band at 745 cm^{-1} corresponds to the C_4-O skeletal vibration of a tertiary alcohol, the band at 814 cm^{-1} to the C_3-O skeletal stretch of a secondary alcohol, and the 885 cm^{-1} peak to the C_2-O skeletal mode of a primary alcohol (ethanol).

PETROLEUM PRODUCTS

Liquid hydrocarbons used in the petroleum industry provide an important mixture of organic chemicals, often analyzed by vibrational spectroscopic methods. Gasolines and other fuels are complex mixtures of hundreds of aliphatic and aromatic hydrocarbons, as well as organic additives present for enhancing

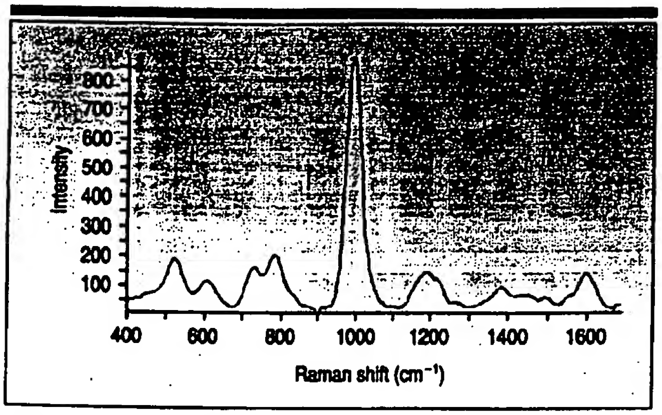

Figure 4. Low-resolution Raman spectrum of a 1:1:1 mixture of benzene, toluene, and xylene isomers.

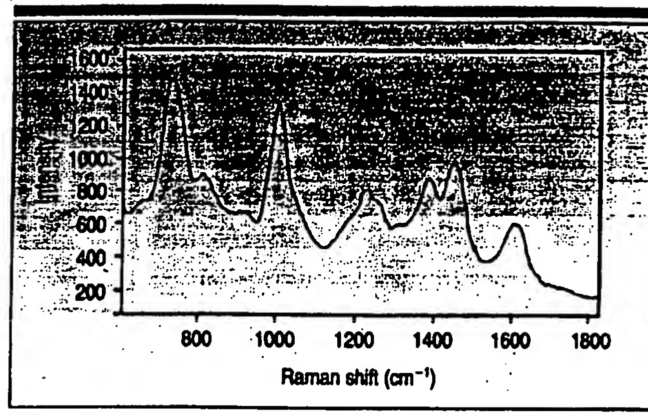

Figure 5. Low-resolution Raman spectra of a commercial 93-octane gasoline.

fuel performance. To demonstrate LRRS's capability we have examined both the common groupings of hydrocarbons often analyzed in petroleum products, along with a sampling of gasolines directly.

The simplest characterization of fuels is in the identification of aromatics and aliphatics in the mixture. Raman is particularly effective in picking up aromatic ring structures as seen in the example of a toluene/hexane mixture. Toluene and *n*-hexane (JT Baker, Phillipsburg, NJ) were mixed as received in the ratio of 1:1 (v/v). We placed 5 mL of the solution in an amber glass cuvette and used an immersion fiberoptic probe to acquire the Raman spectrum. Figure 3 shows the low-resolution Raman spectrum of the mixture solution.

The most prominent band, occurring at 1001 cm^{-1}, arises from the symmetrical (triagonal) ring breathing mode of a monosubstituted benzene. The small shoulder to this band at 1031 cm^{-1} is associated with the in-plane CH deformation in toluene (2). The 785 cm^{-1} peak corresponds to a monosubstituted benzene ring vibration. The aliphatic component of the solution is represented by the band at 1450 cm^{-1}, the CH_2CH_3 deformation mode that characterizes *n*-alkanes. Despite the low resolution, all of the above bands, which characterize the solution, are still visible.

The aromatic composition of fuels is further characterizable by Raman spectroscopy on the basis of the identifying ring vibrational modes that are strong scatterers in the Raman spectrum. An example is the so-called BTEX mixture, benzene/toluene/xylene run on the Raman instrument at low resolution. Benzene (EM Science, Gibbstown, NJ), toluene (JT Baker), and xylene (a mixture of three isomers; JT Baker) were mixed as received at room temperature at 1:1:1 (v/v/v). We recorded a Raman spectrum of the mixture on the R-2000 system with an integration time of 30 s (one scan) and the laser power set at 420 mW (Figure 4). In the mixture the strong band at ~1000 cm^{-1} indicates the presence of the monoaromatic ring. The ring systems are further identified through the peaks at 729 cm^{-1} (xylene) and 785 cm^{-1} (toluene). All such peaks are readily resolved using any laser system, single or multimode, for the excitation source.

In essence, the LRRS approach relies on the fact that only certain spectral features are required to be fully resolved to identify the components in an organic sample. This point is best appreciated in

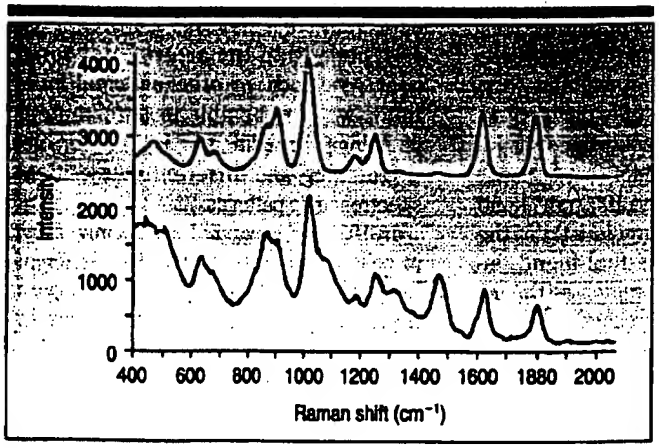

Figure 6. (upper) Low-resolution Raman spectrum of benzyl peroxide powder; (lower) low-resolution Raman spectrum of commercial skin cream.

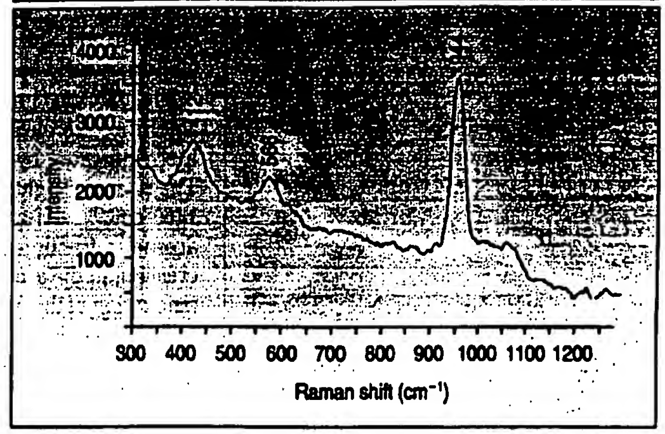

Figure 7. Low-resolution Raman spectrum of a postmortem sample of calcified human aortic valve segment.

the examples of aromatic and aliphatic mixtures, such as the BTEX and hydrocarbon fuel spectra in Figures 3 and 4. In a toluene and xylene mixture the band at 1000 cm^{-1} identifies presence of the aromatic ring, which is then further differentiated by the 728 cm^{-1} band (xylene) and the 785 cm^{-1} band (toluene). Note that in these spectra the toluene/xylene ratio is clearly determined despite the fact that the two usual high-resolution Raman features at 1002 cm^{-1} (toluene) and 1013 cm^{-1} (xylene) are not resolved at all in the LRRS spectrum.

Finally, examples of the hydrocarbon fuels themselves further illustrate the same point concerning the capability of LRRS in sample identification and characterization. Figure 5 depicts the LRRS of a 93-octane grade of gasoline. In many cases aromatics are blended into gaso-

lines to enhance their octane rating (3,4). Even in the LRRS spectra of these fuels, one can clearly see the aromatic fraction in the 1000 cm^{-1} region fully distinguishable from the olefinic background of the fuels indicated by the 1450 cm^{-1} band. The relative heights of the 1000 cm^{-1} and 1450 cm^{-1} band are characteristic of the aromatic fraction of the fuel blend, increasing in the aromatic region as the octane rating of the fuel increases (3,5).

MEDICAL APPLICATIONS: ANALYSIS OF SKIN CREAMS

Skin cream manufacturers are concerned with the performance of their products. One important characteristic is how fast the lubricating ingredients of the cream are absorbed into the skin, and this can be determined easily with LRRS. In many skin creams, the lubricating ingredient is a petroleum-based component characterized by aromatic peaks and hosted in an olefinic. Figure 5 shows an example of how LRRS can be used to monitor the active ingredients of a cream as it is manufactured, then applied to and absorbed by the skin. The upper spectrum in Figure 5 corresponds to the skin-lubricating component of certain skin creams — benzoyl peroxide, a white powder. As with the fuels, the aromatic content of the benzoyl peroxide is characterized by the peak around 1000 cm^{-1}, typical of monoaromatic ring systems. The lower spectrum in Figure 5 corresponds to the glossy white skin cream itself, in this case, a mixture of the lubricating white benzoyl peroxide powder hosted in a placebo cream. All of the peaks characterizing the benzoyl peroxide's aromatic content are still clearly visible. In addition, the olefinic background of the host placebo is clearly indicated by the peak at 1450 cm^{-1}. The concentration of benzoyl peroxide in the cream can easily be determined from the ratio of the height of the aromatic peak at 1000 cm^{-1} to that of the olefinic peak at 1450 cm^{-1}.

Although the results are not presented here, LRRS can be used to monitor the concentration of the lubricating component, benzoyl peroxide, in the skin cream as the cream is applied to and absorbed by a person's skin.

MEDICAL APPLICATIONS: ANALYSIS OF HUMAN AORTIC VALVES

Several research groups have used light scattering for examination and identification of diseased sites within the body. Through the use of catheters containing optical fiber bundles for evaluating a tissue site within the arterial network, heart, stomach, or other internal locations, we may be able to determine a pathological condition by looking for distinguishing and differentiable optical spectroscopic patterns.

In 1987 our group at Boston University, in collaboration with Dr. Jeffrey Isner of St. Elizabeth's Hospital in Boston, was the first to use Raman spectroscopy in the evaluation of diseased sites of cardiovascular tissue (6,7). The advances in the design of compact systems for Raman spectroscopy — particularly LRRS — makes what was considered a laboratory curiosity in 1987 a potentially significant clinical tool now (8).

As an example of such tissue analysis, we examine a diseased segment from a human aortic valve, a valve whose ability to function had been severely compromised by calcium deposits, leading to aortic stenosis. Directing the Raman R-2000 Visionex fiber probe at the surface of such a diseased valve segment results in the LRRS Raman signature spectrum shown in Figure 7. The dominant feature seen in the spectrum at 944 cm^{-1} stands out clearly against the spectral background and is completely absent in healthy tissue samples. The peak at 944 cm^{-1} can be identified by comparison with Raman spectra of solid calcium hydroxyapetite and is a phosphate vibrational mode of the mineralized mass at the diseased site on the aortic valve.

In identifying the presence of the 944 cm^{-1} band, even against the background of other scattering centers, the signature peak of the diseased site is unmistakable. And higher resolution in the Raman spectrum would clearly add nothing to the capability of the measurement for identification and localization of the calcific deposit marking the source of the disease.

Raman spectroscopy is at its beginning point in medical applications. The main impediment to using vibrational analysis for medical applications has been equipment access to the patient and suitable interfacing with the patient's tissue. Because of the less demanding nature of the equipment and the use of optical fibers for delivery and collection of the light signal, LRRS provides a major leap forward in such applications.

CONCLUSIONS

Summarizing the experience of the LRRS examples above we can make the follow-

ing concluding observations. In none of the above spectra is the resolution of the system chosen to make the LRRS measurement less than ~30 cm^{-1}. There will no doubt be cases in which the LRRS measurement is not of sufficiently high resolution to make the required analysis. But, as in the case of mid-IR, it is not always necessary to have the ultimate in spectroscopic resolution to reach the analytical conclusion required. As in the case of near-IR, less may be sufficient when it comes to the employment of a spectral analysis, particularly when cost factors are considered.

The features of the displayed LRRS examples are clearly defined only to an arbitrary resolution standard. Further lowering of the LRRS resolution threshold may still support the analysis required. Improvement through the use of chemometrics analysis methods, as done routinely in near-IR analysis, may present even greater simplification of the LRRS approach as, for example, by design of a purely filter-based Raman system (no dispersion elements at all). Our conclusion is that LRRS has a powerful future in routine chemical analysis, once the real spectral requirements of a specific Raman-based analysis are fully understood.

ACKNOWLEDGMENT

This work has been supported in part at the Boston University Photonics Center by DOD contract number DAAM01-97-C-006.

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Richard H. Clarke *is a professor of chemistry, a member of the Photonics Center faculty at Boston University, and chief executive officer of Boston Advanced Technologies, Inc.* **Sameer Londhe** *is a former graduate student in the Department of Chemistry at Boston University.* **M. Edward Womble** *is a former associate director and a member of the faculty of the Boston University Photonics Center, and is now the vice-president and general manager of the Raman Systems Division of Boston Advanced Technologies, Inc.* ◆